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Cis-vaccenic acid and the Framingham Risk Score predict chronic kidney disease: the Multi-ethnic Study of Atherosclerosis (MESA)

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SUMMARY

Introduction—Data on the associations of fatty acids with chronic kidney disease (CKD) are sparse.

Materials and Methods—We performed a cross-sectional study of 2792 men and women from the MESA cohort of African-American, Caucasian, Chinese and Hispanic adults without known cardiovascular disease. Plasma phospholipid fatty acid proportions were associated with estimated glomerular filtration rate (eGFR) and the albumin/creatinine ratio.

Results—Cis-vaccenic acid (18:1*n*-7), adjusted for other fatty acids using multivariate logistic regression (CI: 1.0–1.4), and step-wise logistic regression (CI: 1.02–1.42), was positively associated with reduced eGFR. The Framingham Risk Score, when adjusting for fatty acid proportions and demographic factors, was positively associated with CKD as measured by the eGFR and the albumin/creatinine ratio.

Discussion and Conclusions—Plasma phospholipid proportions of the 18 carbon monounsaturated cis-vaccenic acid {18:1*n*-7}) and the Framingham Risk Score are associated with kidney function. The potential role of 18:1*n*-7 in the development of CKD warrants further investigation.

Keywords

Fatty acids; chronic kidney disease; Framingham Heart Disease Risk Score; 18:1*n*-7; cisvaccenic acid; monounsaturated 18 carbon fatty acid

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INTRODUCTION

Chronic kidney disease (CKD) is reaching epidemic proportions worldwide[1,2]. The National Kidney Foundation's Kidney Disease Outcome Quality Initiative (NKF-K/DOQI) published criteria for defining and staging CKD in 2002[3]. Stages 3, 4 and 5 represent significant kidney impairment encompassing Glomerular Filtration Rate (GFR) of 30–59 ml/min, 15–29 ml/min, and less than 15 ml/min or dialysis dependence, respectively. An estimated fifteen and a half million Americans (7.7% of the population) are afflicted with stage 3 CKD, and 700,000 (0.35%) with stage 4[4]. The number of patients with end-stage CKD or receiving dialysis for end stage CKD was approximately 540,373 adult patients in 2008[5]. CKD remains an important risk factor for cardiovascular disease and individuals with CKD should be targeted with aggressive prevention measures[6].

Given the overlap between cardiovascular disease and CKD risk, these data support the need to investigate the ability of fatty acid models to predict prevalent and incident CKD. Although lipoproteins have been associated with CKD, the role of fatty acids has not been established[7,8]. One recent study of elderly Italians demonstrated that a higher level of plasma unsaturated fatty acids predicted a less steep decline in GFR[9]. Similar data for younger individuals have been lacking. Due to the fact that many fatty acids are determined primarily by diet, lifestyle modification may have implications for public health strategies for the prevention of CKD. Using a cross-sectional study design, we investigated the association between plasma phospholipid fatty acids and CKD in a relatively young population within the Multi-Ethnic Study of Atherosclerosis. We hypothesized that plasma phospholipid fatty acid proportions, in a model created de novo within the MESA dataset, are associated with CKD as defined by either the estimated GFR (eGFR) <60 ml/min/1.73 m² or a spot albumin/creatinine ratio ≥30 mg/g, which defines microalbuminuria.

METHODS

Study Participants

MESA is a prospective, population-based study designed to investigate the prevalence, risk factors, and progression of subclinical cardiovascular disease in a multi-ethnic cohort in the United States[10,11]. Its study design and methods have been described[10]. Between July 2000 and July 2002, 6814 participants aged 45–84 years were recruited from 6 U.S. communities: Forsyth County, NC; New York, NY; Baltimore, MD; St. Paul, MN; Chicago, IL; and Los Angeles, CA. By taking into account the race/ethnic distribution in each community, field center-specific recruitment procedures were implemented to achieve pre-specified age, gender, and race/ethnicity proportions. Exclusion criteria included a history of clinical cardiovascular diseases, pregnancy, and weight >300 pounds (136 kg). The MESA study was approved by the institutional review board from all participating study sites. All participants gave informed consent. The MESA study included 52.8% female, 38.5% white, 27.8% black, 21.9% Hispanic, and 11.8% Chinese-American participants. Full details of the MESA study population have been described elsewhere[10].

For the present analysis, we considered a subgroup of 2,852 MESA participants who had plasma phospholipid fatty acid profiles measured at baseline. These participants were chosen to equally represent the four ethnic groups (~720 each) when the first MESA Family genotyping project was undertaken. Individuals with missing components of the general cardiovascular disease (CVD) Framingham Risk Score (FRS), eGFR, or the albumin/creatinine ratio were deleted. To take advantage of the richness of data in the MESA 1000 Study, MESA 1000 participants were first chosen as part of the 2880, and the remaining ~1880 were picked randomly to reach 720 in each ethnic group. Three participants were missing data for eGFR, 8 were missing gender, and 1 was missing lipid measurements. Eight

participants had a urinary albumin/creatinine level >300 mg/g and were also excluded from the analysis due to possible nephrotic syndrome. Thus, data from 2792 participants were used for the analyses. Due to differences in recruitment rates, the demographic characteristics of this subgroup were slightly different from the full MESA cohort: younger (61.0 vs. 62.3 years), less likely to be male (46.5% vs. 47.6%), and less likely to be of white (25.7% vs. 47.4%), or black (24.5% vs. 30%) race/ethnicity and more likely to be Chinese-American (25% vs. 2.6%), or Hispanic (24.7% vs. 20%).

Exposure and outcome variables

All 29 of the plasma phospholipid fatty acids in the MESA database, including all omega-3 (*n-3*) (specifically, polyunsaturated fatty acids including 18:3*n-3*, 20:5*n-3* and 22:6*n-3*), omega-6 (*n-6*), and omega-9 (*n-9*), as well as total cis and trans fatty acids, were included in the initial analyses. The approach of calculating the percent of each fatty acid of total fatty acids has been used in several previously published reports[12–14]. The FRS was used for the estimation of general cardiovascular disease events as it predicts the 10 year risk of cardiovascular disease events, defined as one of the following: coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease and heart failure[15]. The algorithm was created from a prospective cohort from Framingham, Massachusetts, and is an update of the traditional (FRS) for “hard” events of myocardial infarction[16]. This newer version was chosen as it includes more cardiovascular events and disease outcomes and allows for a more precise estimate of risk from diabetes mellitus by providing a beta coefficient.

Serum creatinine was measured by rate reflectance spectrophotometry using thin film adaptation of the creatine amidinohydrolase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY 14650) at the Collaborative Studies Clinical Laboratory at University of Minnesota Medical Center, Fairview (Minneapolis, MN). The reference range in adult females is 0.4 – 1.1 mg/dL and in adult males is 0.5 – 1.2 mg/dL. The laboratory CV is 2.2%. All creatinine measurements for the Modification of Diet in Renal Disease (MDRD) Study were performed at Cleveland Clinic Labs using a CX3 assay. The Vitros analyzer used was previously calibrated to a CX3 machine with the Cleveland Clinic lab and the results were nearly identical. Based on calibration, all serum creatinine values were adjusted using the following regression formula: adjusted creatinine = $0.9954 \times (\text{serum creatinine}) + 0.0208$. eGFR was calculated with the Modification of Diet in Renal Disease formula using indirectly calibrated serum creatinine: eGFR_{SCR} (Modification of Diet in Renal Disease GFR prediction equation): $\text{eGFR} = 186.3 \times (\text{serum creatinine concentration})^{-1.154} \times (\text{age})^{-0.203} \times 1.212 (\text{if black}) \times 0.742 (\text{if female})$ [17,18]. According to recommendations of the National Kidney Foundation[3], we classified patients with CKD as having either an eGFR <60 ml/min/1.73 m² or a urinary albumin/creatinine ratio of >30 mg/g, separately, as abnormalities of each are markers for different forms of renal pathophysiology and less than 100% correlation is present between these estimators of renal function in patients[19–21].

Fatty acid extraction and analyses

Fasting blood samples were collected and processed using a standardized protocol[10,22]. Details of sample shipping and sample repository are described elsewhere[22]. Phospholipid fatty acids were measured in EDTA plasma which had been frozen and stored at –70°C. Fatty acid analyses were performed at the University of Minnesota (Minneapolis, MN) and the laboratory procedure for fatty acid extraction is described in detail elsewhere[23]. Briefly for the extraction of plasma phospholipid fatty acids, lipids were extracted using chloroform/methanol, and thin layer chromatography was used to separate the lipid fractions. The phospholipid fraction was used to produce methyl esters and the fatty acids

were assessed by gas chromatography using a flame ionization detector. The concentration of each fatty acid was expressed as a percentage of total fatty acids.

Statistical methods

All fatty acid variables were tested for normality using scatter plots, the Shapiro-Wilk, and Kolmogorov-Smirnov statistics; since most of the variables violated the normality assumptions, bivariate analyses with the outcome (GFR) were performed using Mann-Whitney Wilcoxon tests (nonparametric two sample t-tests). Fatty acid variables with a p -value <0.20 in bivariate analyses with either eGFR or albumin/creatinine ratio were chosen for initial inclusion in the logistic regression model with eGFR < 60 ml/min/1.73 m² as the dependent variable. Tests for trend for continuous variables were assessed utilizing Spearman correlation coefficients. Based on a VIF > 10 , 18:1trans was highly collinear with 18:1n-9 cis and was removed from the final multivariate models.

Demographic and clinical variables chosen for inclusion in the multivariate models were determined based on *a priori* correlation with cardiovascular disease and bivariate associations with eGFR < 60 ml/min/1.73 m² resulting in a p -value <0.2 . These included age, gender, race/ethnicity, current smoking status, non-HDL cholesterol, systolic blood pressure, the use of medications for blood pressure, diabetes (based on history, use of medications, or glucose), and waist /hip ratio. The following multivariate logistic models were constructed with eGFR < 60 ml/min/1.73 m² as the dependent variable: 1) fatty acid variables significant in bivariate analyses; 2) demographic variables; 3) FRS variables; 4) FRS + demographic variables; 5) FRS + fatty acid variables significant in bivariate analyses; 6) FRS + bivariate results + demographic variables; 7) stepwise regression including only fatty acid variables; 8) and stepwise regression including fatty acid variables + demographic variables. Presented odds ratios were scaled to the interquartile range of the fatty acid variables.

With a standard deviation of the fatty acids eicosapentaenoic acid (EPA; 20:5n-3) + docosahexaenoic acid (DHA; 22:6n-3) of 1, an alpha of 0.05, and an estimated 100 participants per group, the power to detect a difference of 2 in the EPA+DHA means between groups with eGFR ≥ 60 mL/min/1.73 m² versus eGFR <60 mL/min/1.73 m² is $>99\%$. SAS 9.2 was used.

RESULTS

Characteristics of enrolled participants are displayed in Table 1. A person with a calculated eGFR <60 ml/min/1.73 m² was categorized as a “CKD participant” and someone with an eGFR ≥ 60 ml/min/1.73 m² as a “non-CKD participant”. The majority of individuals were over the age of 60, female, non-Caucasian, and overweight. The average age was higher for the CKD participants than the non-CKD participants and more CKD participants than non-CKD participants were female and Caucasian. Although body mass index did not significantly differ between the two groups, waist circumference was lower in the CKD group than the non-CKD group. Lipid medication use, the presence of hypertension and the use of antihypertensive medications were more common in the CKD group than the non-CKD group. Fewer participants in the CKD group than in the non-CKD group were active smokers. Participants with CKD tended to be less educated and have lower income than participants without CKD but these differences were of borderline statistical significance. Triglycerides were significantly lower in participants with CKD than those without CKD, although both groups had triglycerides lower than the National Cholesterol Education Program's [24] borderline concentration of 150 mg/dL. Total cholesterol, HDL, and LDL concentrations did not differ significantly. Urinary median and interquartile ratio

concentrations of albumin/creatinine were significantly higher in the CKD group than in the non-CKD group. In Table 2 categorical proportions of each fatty acid are displayed.

Table 3 shows the results of the logistic regression analyses of the association between the percentage of fatty acids (as continuous variables with means represented) measured in the group with $\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$ and $\text{eGFR} \geq 60 \text{ ml/min/1.73 m}^2$. Those fatty acids significantly and positively associated with $\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$ using a p -value < 0.1 , were 18:1 *n*-9 *cis*, 18:1 *n*-7 *cis*, and the sum of 18:1 *n*-9 *cis*, 18:1 *n*-7 *cis*, and 18:1 *n*-6 *cis* expressed as 18:1 *cis*. All other fatty acid percentages were not significantly associated with $\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$.

Table 4 displays the results of the logistic regression analyses of the association between percentages of fatty acids measured in the sample of MESA participants with and without microalbuminuria and any eGFR . Those fatty acids with increased percentage significantly and positively associated with microalbuminuria (albumin/creatinine ratio 30–300), using a p -value < 0.1 , was 16:0; and using a p -value < 0.2 , 18:3 *n*-6. Those with increased percentage positively associated with an albumin/creatinine ratio $< 30 \text{ mg/g}$, using a p -value < 0.1 , were 15:0, 18:0, 18:1 *n*-6 *cis*, 18:1 *n*-6 *trans*, 18:1 *n*-7–9 *trans*, 18:1 *trans* (the sum of 18:1 *n*-7–9 *trans* and 18:1 *n*-6 *trans*), 18:2 *n*-6 *trans/cis*, 20:1 *n*-9, and total *trans* fatty acids. With p -value < 0.2 , 16:1 *n*-7 *trans* and 18:3 *n*-6 had increased percentage negatively correlated with a reduced (normal) ratio.

Table 5 shows the mean percentages of each fatty acid across four eGFR categories along with p -values addressing trends among these categories. These data support the logistic regression data demonstrating that the fatty acids 18:1 *n*-9 *cis* and 18:1 *n*-7 *cis*, as well as the sum of 18:1 *n*-9 *cis*, 18:1 *n*-7 *cis* and 18:1 *n*-6 *cis* (18:1 *cis*) have higher mean percentages in individuals with lower eGFR values. In addition, the trend for mean percentages of other fatty acids associated with the albumin/creatinine ratio are supported by the data in Tables 3 and 4. These fatty acids include 15:0, 18:1 *n*-7–9 *trans*, the sum value of 18:1 *trans* including 18:1 *n*-7–9 *trans* and 18:1 *n*-6 *trans*, 18:2 *n*-6 *trans/cis*, 20:1 *n*-9, and total *trans* fatty acids (sum of 16:1 *n*-7 *trans*, 18:1 *n*-7–9 *trans*, 18:1 *n*-6 *trans*, 18:2 *n*-6 *trans/trans*, 18:2 *n*-6 *cis/trans*, 18:2 *n*-6 *trans/cis*).

Data from adjusted statistical models with $\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$ as the outcome are represented in Table 6. When adjusting for other fatty acids associated with eGFR , none of the fatty acids were significantly correlated with eGFR (p -values > 0.05) except for 18:1 *n*-7 (CI 1.0–1.4). Although, when adjusting for race/ethnicity, smoking, non-HDL cholesterol, systolic blood pressure, the use of blood pressure medication, the presence of diabetes mellitus, and waist-to-hip ratio, a high percentage of the fatty acid 18:1 *n*-7 *cis* was not significantly associated with an increased risk of reduced eGFR ($< 60 \text{ mg/dL}$), it was when using a step-wise regression model. A high FRS was also positively associated with an increased risk of an $\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$ whether or not race/ethnicity and the waist-to-hip ratio were included in the model. It remained positively associated with $\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$ when fatty acids were included in the model. No fatty acids were significantly associated with $\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$ when FRS was included.

Data from adjusted statistical models with microalbuminuria as the outcome are represented in Table 7. When adjusting for other fatty acids associated with the albumin/creatinine ratio higher percentages of 20:1 *n*-9 was statistically (p -value < 0.05) associated with a lack of albuminuria (a ratio $< 30 \text{ mg/dL}$). When adjusting for race/ethnicity, smoking, non-HDL cholesterol, systolic blood pressure, the use of blood pressure medication, the presence of diabetes mellitus, and waist-to-hip ratio, elevated percentages of any fatty acid were not significantly associated (p -value < 0.05) with the albumin/creatinine ratio. A high FRS was

positively associated with an increased risk of microalbuminuria whether or not race/ethnicity and the waist-to-hip ratio were included in the model. When adjusting for the FRS, increased percentages of **20:1n-9** were statistically ($p<0.05$) associated with a decreased risk of microalbuminuria.

The relationships of the fish oil-derived omega-3 (20:5n-3, 22:5n-3, 22:6n-3), 18:1n-7 cis, and 20:1n-9, fatty acid relationships with CKD were analyzed as continuous variables within the ethnic subgroups of Caucasians (n=717), Asians (n=699), African-Americans (n=685), and Hispanics (n=691) {data not shown}. None of the n-3 fatty acids were associated with eGFR for any ethnicity. In bivariate analyses, 22:6n-3 was positively associated in Asians with a normal albumin/creatinine ratio ($p<0.05$). This association was not significant for any n-3 fatty acids within any of the other ethnic groups ($p>0.05$). When adjusted for other variables in Table 7: for all of the fatty acids, for all of the fatty acids and demographic variables, and for all of these fatty acids and the Framingham Risk Score, 22:6n-3 was not associated with the albumin/creatinine ratio ($p>0.05$). 18:1n-7 cis, 18:1n-9 cis, and 20:0 were not associated with eGFR using multivariate regression including these 3 fatty acids ($p>0.05$) but 18:1n-7 was associated with a reduced eGFR in Asians when demographic variables were also included ($p=0.012$). This was not true for the 18:1n-9 cis, and 20:0 fatty acids ($p>0.05$). 18:1n-7 in multivariate regression including 18:1n-9 and 20:0 was positively associated with the Framingham Risk Score ($p=0.048$) in Asians but not in the other ethnicities. In step-wise regression, 18:1n-7 was positively associated with reduced eGFR in Asians with borderline significance ($p=0.053$) but not with the other ethnic groups. Of those fatty acids in Table 7, 16:1n-7 trans was positively associated with the albumin/creatinine ratio ($p=0.007$), adjusting for the other fatty acids in multivariate regression, in Caucasians but not within the other ethnic groups. This was not significant when demographic variables were included.

DISCUSSION

While there are established relationships between fatty acids and cardiovascular disease[25,26], the role of fatty acids in the development of human CKD has not been clearly established[7,8,27]. While risk is generally straightforward for less complicated CVD, the presence of renal disease complicates risk so that usual risk factors are not consistently predictive of CVD. In the other hand, because their concentrations are established by multiple factors including nutritional status, inflammatory status, genetic factors and others, tissue fatty acid proportions are a potential reservoir of information related to pathological risk, and we have confirmed their value in acute coronary syndromes[12,13,28]. As the pathophysiologic process is similar for CKD and CVD, through this current cross-sectional study we investigated the relationship of blood proportions of many fatty acids with the presence or absence of chronic kidney disease in a large, generally healthy, young, and ethnically diverse cohort of US citizens. In general, few fatty acids were valuable in predicting renal disease when measured either by filtration status or by proteinuria. Exceptions were the rarely analyzed monounsaturated octadecanoids 18:1n-7 cis and 18:1n-6 cis along with 18 carbon trans fatty acids and 20:1n-9.

In contrast to our findings, other studies have shown univariate relationships with eGFR[9,29]. The InCHIANTI study (Aging in the Chianti Area) enrolled participants who were at least 65 years of age (mean age >70) from two small towns in Italy. In this study, baseline fatty acids were not nearly as predictive of baseline serum creatinine as they were of creatinine at 3 years of follow-up[9]. Higher concentrations of total plasma polyunsaturated fatty acids, n-3 fatty acids, n-6 fatty acids, as well as 18:2n-6, 18:3n-3, and 20:4n-6 were strong independent predictors of less steep decline in creatinine clearance from

baseline to follow-up. Individuals with higher plasma polyunsaturated fatty acids had a lower risk of developing renal disease, defined by a creatinine clearance <60 mL/min, during 3 years of follow-up. In a pilot study, we found positive correlations between eGFR and 16:1n7, 18:0, 18:3n-6, 20:2n-6, 20:2n-6, and n-3 polyunsaturated fatty acids[29]. A single fatty acid, oleic acid, was inversely related to eGFR. Other studies have suggested that polyunsaturated fatty acids may be exerting protective effects on kidney function through mechanisms including reduced inflammation and fibrosis[30]. Through our current cross-sectional study, we investigated the relationship of blood concentrations of many fatty acids with the presence or absence of CKD in a larger, generally healthy, younger, and ethnically diverse cohort of US citizens.

Cis-vaccenic acid (18:1n-7 *cis*) is a monounsaturated and non-essential n-7 fatty acid stereoisomer of 18:1n-7 *trans*[31]. This *cis* fatty acid has been shown to be derived from intestinal flora[32] and inhibit neoplasm formation. What is also interesting is that 18:1n-7 *trans* is found in milk and has properties that appear to improve health[33]. The fact that this *cis* fatty acid was positively associated with reduced kidney function in the current study is of interest as fatty acids with a *cis* conformation are generally considered healthy and *trans* fatty acids considered unhealthy[34]. Of interest is also its positive relationship with reduced eGFR only in Chinese-Americans as it may be that reducing it would have beneficial effects within this population. However, we are not aware of any published evidence that this fatty acid is associated with CKD.

Erucic acid, 20:1n-9 (a monounsaturated and non-essential n-9 fatty acid), can be created from saturated fatty acids and is found in a variety of plant oils[35]. We are not aware of published data correlating this fatty acid with kidney disease. In one study, multivariate linear regression analyses of individual fatty acids as covariates revealed positive associations between heart rate and levels of erucic acid ($p = .007$)[35], and if causal, increasing erucic acid would contribute to cardiovascular stress in these participants. In our study, it was associated with albuminuria when adjusting for other fatty acids. However, its association with CKD was not present when adjusting for other factors associated with vascular disease and this association was not present for a particular ethnic group.

After more than 25 years of research, including randomized controlled trials, the benefits of n-3 polyunsaturated fatty acids in the treatment of kidney disease remain unclear[27]. This is true despite the fact that *in vitro* and *in vivo* studies support the efficacy of n-3 polyunsaturated fatty acids on reducing inflammatory pathways involved with the progression of kidney disease as well as lowering blood pressure, risk of cardiovascular disease, and risk factors for CKD[36]. However, clinical investigators have focused predominantly on immunoglobulin A (IgA) nephropathy. These studies have had conflicting results, which may relate to the diversity of n-3 fatty acids, their doses, the size of the cohort studied, and the duration of therapy. A recent trend has been the investigation of their relationship with polycystic kidney disease, lupus nephritis, and other glomerular diseases, with limited potentially beneficial associations found[27]. In our study, the fish oil-derived 22:6n-3 fatty acid was associated with a lack of albuminuria in Chinese-Americans but no association with CKD in the other ethnic groups. This is true despite the fact that fish intake amongst Chinese Americans approximates that for Caucasians within MESA[37].

Recent studies have demonstrated that reduced eGFR and higher levels of albuminuria are risk factors for hypertension and diabetes mellitus[38]. Other studies have shown that estimated eGFR and albuminuria are strongly and independently associated with progression to end stage renal disease[19,20] with hazard ratios for eGFR 45 to 59, 30 to 44, and 15 to 29 mL/min per 1.73 m², 6.7, 18.8, and 65.7, respectively ($p < 0.001$ for all), and for micro- and macroalbuminuria being 13.0 and 47.2 ($p < 0.001$ for both). It has also been

demonstrated that diabetes, hypertension, smoking, male gender, depression, cardiovascular disease, obesity, dyslipidemia, physical activity and education do not add to the predictive information provided by eGFR and albuminuria data[19]. Similarly, the albumin/creatinine ratio is a very strong predictor of CKD[3,39]. Vascular disease is the likely cause of reduced GFR and albuminuria in older adults with diabetes, hypertension, or both found in a large fraction of those with CKD[38]. Since blood fatty acid content is associated with cardiovascular disease[34], similar correlation with CKD is likely pathophysiologically. In addition, since the predictability of eGFR and the albumin/creatinine ratio are not outweighed by the presence of traditional cardiovascular risk factors, we assessed associations with both eGFR and the albumin/creatinine ratio to estimate the long-term effects of fatty acids on kidney disease.

Although the FRS is widely used and a reliable predictor of cardiovascular disease[15], studies to determine its relationship with CKD have been limited[40]. One study of 505 healthy Chinese men and women, age 35–93 years, investigated the relationship between the Framingham risk score (FRS) with respect to calculated renal function. As the FRS level increased, GFR and creatinine clearance decreased ($p<.01$). There were significant inverse correlations between FRS and GFR and creatinine clearance rate. However, the relationship between FRS and creatinine clearance was lost after controlling for age and other confounding variables. Our current study demonstrated that creatinine clearance and GFR were related to the FRS when adjusting for fatty acids, ethnicity, demographic, and clinical factors.

One potential limitation of the current study is that plasma phospholipids, regardless of their parent glycerolipid, were measured instead of total plasma fatty acids. In our own observation, we have found that total plasma fatty acids are better correlated with red blood cell fatty acids[29]. In general, red blood cell fatty acids are considered the best tissue fatty acid pool to measure, and the standardization of this pool is well documented[25,41]. However, not every study collects this fraction and so plasma phospholipids are thought to be a good substitute. The potential for biases that arise in a cross-sectional study are also a potential limitation. A large number of statistical tests are performed, potentially leading to type 1 error as we did not adjust the p-values for multiple testing. We also acknowledge that, except for the fish oil-derived 20:5n3 and 22:6n-3 fatty acids, we did not have specific, biologically based a priori hypotheses regarding which fatty acid(s) would be associated with renal insufficiency. It is also important to note that, given study and design limitations, these results do not exclude the possibility that specific fatty acids may be renoprotective or harmful to the kidney.

In conclusion, plasma phospholipid fatty acid proportions did not substantially predict renal disease in this analysis. A single monounsaturated fatty acid, erucic acid (20:1n-9), was useful in predicting the extent of proteinuric renal disease but this association disappeared after adjusting for demographic factors. The other monounsaturated fatty acid cis-vaccenic acid (18:1n-7) was positively associated with reduced eGFR when adjusting for ethnicity, clinical and demographic factors. Its potential adverse association with eGFR in Chinese-Americans is of interest as no known reason for this to be present only in this ethnic group represented in this study exists. The potential etiologies of these relationships are unclear but deserve further study. An association between the cardioprotective fish oil-derived fatty acid 22:6n-3 and a lack of albuminuria was present in Chinese Americans and not within the other ethnicities represented. This association should also be further studied given that higher n-3 consumption amongst Chinese-Americans than for many other Americans may be protective.

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Information on Re-engineering the Clinical Research Enterprise can be obtained from <http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp>.

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TABLE 1

Participant Characteristics

Variable	CKD Subjects (N=233)	Non-CKD Subjects (N=2559)	p-value
Age (yr)	69.4 (8.5)	60.7 (9.9)	<.0001
Male (%)	89 (38%)	1209 (47%)	0.008
Caucasian (%)	86 (37%)	631 (25%)	<.0001
Body mass index (kg/m ²)	28.2 (5.2)	27.8 (5.5)	0.18
Waist circumference (cm)	99.1 (13.4)	96.3 (14.3)	0.0001
Family history of premature CHD	94 (43%)	911 (38%)	0.13
Lipid medication use	55 (24%)	373 (14%)	0.0002
Blood pressure medication use	127 (54%)	745 (29%)	<.0001
Hypertension (by history)	142 (61%)	874 (34%)	<.0001
Diabetes mellitus	34 (14%)	277 (11%)	0.08
Currently smoking	19 (8%)	357 (14%)	0.01
Number of alcoholic drinks/week	3.4 (5.8)	4.5 (7.9)	0.1
Highest level of education completed			
Less than high school	57 (24%)	540 (21%)	
High school or GED	52 (22%)	452 (18%)	
At least some college	124 (53%)	1567 (61%)	0.05
Income (past 12 months)			
Less than \$40,000	138 (61%)	1363 (55%)	
\$40,000-less than \$75,000	56 (25%)	607 (24%)	
Greater than \$75,000	33 (14%)	519 (21%)	0.06
Total cholesterol (mg/dL)	196.2 (40.1)	194.2 (34.7)	0.46
Triglycerides (mg/dL)	147.3 (80.8)	133.5 (92.2)	<.0001
HDL cholesterol (mg/dL)	50.6 (14.9)	50.6 (14.2)	0.91
LDL cholesterol (mg/dL)	115.9 (34.9)	117.2 (30.6)	0.46
Urinary albumin/creatinine (mg/dL), median	7.05	5.4	<.0001
Urinary albumin/creatinine (mg/dL), IQR	18.1	7.1	<.0001

SD is an acronym for standard deviation. IQR is an acronym for inter-quartile range

TABLE 2

Categorical Proportions of Each Fatty Acid

Fatty Acid	Min	25%	Median	75%	Max
14:00	0.06	0.2	0.25	0.31	0.75
15:00	0.05	0.13	0.16	0.19	0.53
16:00	19.34	24.28	25.28	26.35	40.12
16:1 <i>n</i> -7 <i>cis</i>	0.12	0.35	0.46	0.61	1.9
16:1 <i>n</i> -7 <i>trans</i>	0.01	0.03	0.05	0.07	0.24
18:00	7.45	12	13.17	14.14	23.71
18:1 <i>n</i> -7 <i>cis</i>	0.75	1.22	1.36	1.52	2.54
18:1 <i>n</i> -6 <i>cis</i>	0.04	0.27	0.45	0.65	2.51
18:1 <i>n</i> -6 <i>trans</i>	0.02	0.18	0.32	0.47	1.5
18:1 <i>n</i> -7-9 <i>trans</i>	0.07	0.56	0.85	1.2	3.75
18:1 <i>n</i> -9 <i>cis</i>	4.28	6.87	7.62	8.42	16.28
18:2 <i>n</i> -6 <i>cis/cis</i>	11.38	19.09	21.27	23.56	36.13
18:2 <i>n</i> -6 <i>cis/trans</i>	0.01	0.04	0.05	0.07	0.18
18:2 <i>n</i> -6 <i>trans/cis</i>	0.02	0.07	0.1	0.14	0.43
18:2 <i>n</i> -6 <i>trans/trans</i>	0.01	0.02	0.03	0.05	0.18
18:3 <i>n</i> -3	0.03	0.13	0.16	0.21	2.54
18:3 <i>n</i> -6	0.01	0.07	0.1	0.13	0.48
20:00	0.06	0.18	0.24	0.3	0.66
20:1 <i>n</i> -9	0.05	0.1	0.12	0.15	0.92
20:2 <i>n</i> -6	0.2	0.33	0.38	0.44	1.22
20:3 <i>n</i> -6	0.93	2.61	3.15	3.77	6.66
20:4 <i>n</i> -6	3.58	10.14	11.83	13.77	22.17
20:5 <i>n</i> -3	0.09	0.5	0.7	1.08	14.46
22:00	0.09	0.35	0.49	0.72	2.26
22:5 <i>n</i> -3	0.37	0.81	0.93	1.08	2.42
22:6 <i>n</i> -3	1.18	3.02	3.99	5.15	10.41
24:1 <i>n</i> -9	0.03	0.39	0.58	0.85	2.75
18:1 <i>cis</i> ***	5.35	8.64	9.47	10.42	19.07

Fatty Acid	Min	25%	Median	75%	Max
18:1trans***	0.1	0.76	1.18	1.65	5.14
18:2trans****	0.05	0.15	0.19	0.24	0.68
total trans	0.22	0.96	1.43	1.96	5.9

* eGFR is an acronym for estimated glomerular filtration rate

** 18:1 cis is an aggregate lipid measure of 18:1*n*-9 cis, 18:1*n*-7 cis, and 18:1*n*-6 cis

*** 18:1 trans is an aggregate lipid measure of 18:1*n*-6t, 18:1*n*-7t

**** 18:2 trans is an aggregate lipid measure of 18:2*n*-6cis/trans, 18:2*n*-6trans/cis, and 18:2*n*-6trans/trans

TABLE 3

Mean Percentages of Each Fatty Acid in Bivariate Analyses with eGFR * Using Logistic Regression

Fatty Acid	eGFR <60 n=233	eGFR 60 n=2559	Odds Ratio (95% CI)	p-value
14:00	0.09	0.09	0.99 (0.83–1.18)	0.9
15:00	0.1	0.11	0.98 (0.84–1.16)	0.85
16:00	0.06	0.05	1.02 (0.87–1.20)	0.8
16:1 <i>n</i> -7cis	0.22	0.17	1.08 (0.93–1.25)	0.33
16:1 <i>n</i> -7trans	0.17	0.14	1.06 (0.87–1.28)	0.57
18:00	−0.11	−0.05	0.89 (0.75–1.06)	0.2
18:1 <i>n</i> -7cis	0.18	0.06	1.20 (1.02–1.42)	0.03
18:1 <i>n</i> -6cis	0.08	0.12	0.95 (0.80–1.13)	0.54
18:1 <i>n</i> -6trans	0.08	0.09	0.97 (0.80–1.17)	0.74
18:1 <i>n</i> -7–9trans	0.15	0.11	1.06 (0.89–1.27)	0.49
18:1 <i>n</i> -9cis	0.15	0.05	1.15 (0.98–1.35)	0.09
18:2 <i>n</i> -6cis/cis	0.07	0.03	1.07 (0.90–1.28)	0.45
18:2 <i>n</i> -6cis/trans	0.25	0.21	1.08 (0.88–1.32)	0.45
18:2 <i>n</i> -6trans/cis	0.1	0.17	0.87 (0.72–1.05)	0.16
18:2 <i>n</i> -6trans/trans	0.18	0.18	1.00 (0.84–1.19)	0.99
18:3 <i>n</i> -3	0.25	0.19	1.04 (0.94–1.16)	0.43
18:3 <i>n</i> -6	0.18	0.14	1.06 (0.91–1.23)	0.45
20:00	−0.02	0.05	0.88 (0.73–1.06)	0.17
20:1 <i>n</i> -9	0.24	0.22	1.01 (0.89–1.16)	0.83
20:2 <i>n</i> -6	0.15	0.12	1.05 (0.88–1.24)	0.58
20:3 <i>n</i> -6	0.03	0.06	0.95 (0.79–1.13)	0.56
20:4 <i>n</i> -6	0.02	0.05	0.96 (0.79–1.16)	0.65
20:5 <i>n</i> -3	0.42	0.47	0.98 (0.90–1.07)	0.69
22:00	0.18	0.19	0.98 (0.82–1.16)	0.79
22:5 <i>n</i> -3	0.06	0.1	0.94 (0.80–1.11)	0.46
22:6 <i>n</i> -3	0.09	0.1	0.98 (0.81–1.18)	0.82
24:1 <i>n</i> -9	0.2	0.19	1.01 (0.86–1.18)	0.92
18:1 cis **	0.15	0.06	1.16 (0.98–1.37)	0.08
18:1trans ***	0.12	0.1	1.04 (0.86–1.24)	0.7
18:2trans ****	0.1	0.14	0.94 (0.81–1.11)	0.48
total trans	0.11	0.1	1.03 (0.85–1.23)	0.7

* eGFR is an acronym for estimated glomerular filtration rate

** 18:1 cis is an aggregate lipid measure of 18:1*n*-9 cis, 18:1*n*-7 cis, and 18:1*n*-6 cis

*** 18:1 trans is an aggregate lipid measure of 18:1*n*-6t, 18:1*n*-7–9t

**** 18:2 trans is an aggregate lipid measure of 18:2*n*-6cis/trans, 18:2*n*-6trans/cis, and 18:2*n*-6trans/trans

TABLE 4

Mean Percentages of Fatty Acids in Bivariate Analyses with Albumin/Creatinine Ratio Using Logistic Regression

Fatty Acid	Albumin/creatinine: 30–300 n=235	Albumin/creatinine: <30 n=2544	Odds Ratio (95% CI)	p-value
14:00	0.1	0.1	1.01 (0.84–1.20)	0.95
15:00	0.02	0.12	0.86 (0.72–1.02)	0.08
16:00	0.17	0.04	1.20 (1.03–1.40)	0.02
16:1 <i>n</i> -7cis	0.15	0.17	0.98 (0.84–1.15)	0.83
16:1 <i>n</i> -7trans	0.08	0.15	0.86 (0.70–1.05)	0.14
18:00	–0.13	–0.04	0.86 (0.72–1.02)	0.09
18:1 <i>n</i> -7cis	0.03	0.08	0.92 (0.78–1.10)	0.36
18:1 <i>n</i> -6cis	0.02	0.12	0.84 (0.70–1.00)	0.05
18:1 <i>n</i> -6trans	–0.02	0.1	0.76 (0.62–0.93)	0.009
18:1 <i>n</i> -7–9trans	0.01	0.12	0.80 (0.66–0.97)	0.02
18:1 <i>n</i> -9cis	0.1	0.06	1.07 (0.91–1.26)	0.4
18:2 <i>n</i> -6cis/cis	0.07	0.03	1.06 (0.89–1.26)	0.52
18:2 <i>n</i> -6cis/trans	0.19	0.22	0.94 (0.76–1.15)	0.55
18:2 <i>n</i> -6trans/cis	0.05	0.17	0.80 (0.65–0.97)	0.02
18:2 <i>n</i> -6trans/trans	0.23	0.17	1.11 (0.94–1.31)	0.22
18:3 <i>n</i> -3	0.18	0.2	0.98 (0.85–1.12)	0.76
18:3 <i>n</i> -6	0.22	0.13	1.11 (0.96–1.29)	0.15
20:00	0.07	0.04	1.06 (0.89–1.27)	0.52
20:1 <i>n</i> -9	0.08	0.24	0.80 (0.66–0.96)	0.02
20:2 <i>n</i> -6	0.15	0.12	1.05 (0.89–1.25)	0.55
20:3 <i>n</i> -6	0.12	0.06	1.11 (0.93–1.32)	0.24
20:4 <i>n</i> -6	–0.01	0.05	0.89 (0.73–1.07)	0.21
20:5 <i>n</i> -3	0.41	0.47	0.97 (0.89–1.07)	0.59
22:00	0.24	0.19	1.09 (0.92–1.28)	0.3
22:5 <i>n</i> -3	0.08	0.1	0.97 (0.82–1.13)	0.68
22:6 <i>n</i> -3	0.12	0.1	1.03 (0.86–1.24)	0.72
24:1 <i>n</i> -9	0.23	0.19	1.05 (0.90–1.23)	0.49
18:1 cis**	0.07	0.06	1.02 (0.86–1.20)	0.86
18:1 trans***	–0.01	0.11	0.78 (0.64–0.95)	0.01
18:2 trans****	0.07	0.14	0.90 (0.77–1.06)	0.21
total trans	–0.01	0.11	0.78 (0.65–0.95)	0.01

* 18:1 cis is an aggregate lipid measure of 18:1 *n*-9 cis, 18:1 *n*-7 cis, and 18:1 *n*-6 cis

** 18:1 trans is an aggregate lipid measure of 18:1 *n*-6t, 18:1 *n*-7–9t

*** 18:2 trans is an aggregate lipid measure of 18:2 *n*-6cis/trans, 18:2 *n*-6trans/cis, and 18:2 *n*-6trans/trans

TABLE 5

Mean Percentages of Fatty Acids by eGFR * Groups

Fatty Acid	eGFR 30-45 n=28	eGFR 45-60 n=202	eGFR 60-90 n=1711	eGFR 90+ n=848	p-value for trend
14:00	0.249	0.262	0.262	0.259	0.16
15:00	0.161	0.167	0.17	0.16	<.0001
16:00	25.579	25.408	25.372	25.417	0.63
16:1n-7cis	0.492	0.522	0.502	0.502	0.17
16:1n-7trans	0.054	0.057	0.057	0.053	0.001
18:00	12.514	13.025	13.041	13.132	0.12
18:1n-7cis	1.541	1.396	1.386	1.366	0.001
18:1n-6cis	0.471	0.482	0.503	0.48	0.08
18:1n-6trans	0.304	0.347	0.352	0.339	0.14
18:1n-7-9trans	0.902	0.945	0.937	0.89	0.004
18:1n-9cis	7.83	7.846	7.723	7.664	0.003
18:2n-6cis/cis	20.804	21.685	21.466	21.317	0.78
18:2n-6cis/trans	0.054	0.058	0.057	0.055	0.14
18:2n-6trans/cis	0.103	0.107	0.113	0.109	0.07
18:2n-6trans/trans	0.033	0.036	0.036	0.034	0.26
18:3n-3	0.157	0.184	0.176	0.176	0.41
18:3n-6	0.115	0.11	0.108	0.109	0.91
20:00	0.27	0.234	0.245	0.247	0.17
20:1n-9	0.136	0.132	0.133	0.127	0.001
20:2n-6	0.408	0.395	0.396	0.389	0.02
20:3n-6	3.068	3.217	3.217	3.242	0.96
20:4n-6	12.49	11.824	11.956	12.101	0.13
20:5n-3	0.738	0.98	0.961	0.991	0.9
22:00	0.63	0.547	0.56	0.565	0.24
22:5n-3	0.908	0.952	0.958	0.957	0.74
22:6n-3	4.345	4.159	4.198	4.234	0.71
24:1n-9	0.91	0.635	0.667	0.67	0.35
18:1 cis**	9.842	9.723	9.61	9.508	0.001

Fatty Acid	eGFR 30–45 n=28	eGFR 45–60 n=202	eGFR 60–90 n=1711	eGFR 90+ n=848	p-value for trend
18:1trans***	1.206	1.292	1.288	1.229	0.01
18:2trans****	0.19	0.199	0.205	0.197	0.06
total trans	1.206	1.293	1.289	1.23	0.01

p-values were generated using Spearman correlations

* eGFR is an acronym for estimated glomerular filtration rate

** 18:1 cis is an aggregate lipid measure of 18:1*n*-9 cis, 18:1*n*-7 cis, and 18:1*n*-6cis

*** 18:1 trans is an aggregate lipid measure of 18:1*n*-6trans, 18:1*n*-7-9trans

**** 18:2 is an aggregate lipid measure of 18:2*n*-6cis/trans, 18:2*n*-6trans/cis, and 18:2*n*-6trans/trans

TABLE 6

Results of Statistical Models with eGFR < 60 mg/dL as the Outcome

Independent Variable	Logistic Regression Models						Step-Wise Logistic			
	*FAs		*FAs+ Demo/Clin		Framingham Risk Score (FRS)		FRS+ Demo/Clin		FRS+ *FAs	
	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI
Fatty Acids										
18:1 <i>n</i> -7 cis	1.18	1.00–1.40	1.12	0.92–1.36					1.15	0.97–1.36
18:1 <i>n</i> -9 cis	1.1	0.94–1.30	0.96	0.79–1.17					1.06	0.90–1.26
20:0	0.89	0.74–1.08	0.94	0.78–1.14					0.91	0.76–1.10
Demographic Variables										
Race (Caucasian ref group)										
Chinese-American			0.61	0.41–0.91			0.69	0.48–0.98		
African-American			0.37	0.24–0.57			0.41	0.27–0.62		
Hispanic-American			0.39	0.26–0.59			0.41	0.27–0.61		
Age			1.08	1.06–1.10			1.07	1.05–1.09		
Male			0.64	0.47–0.87			0.43	0.30–0.61		
Clinical Variables										
Smoking (yes)			0.82	0.49–1.38						
non-HDL cholesterol (mg/dL)			1	1.00–1.01						
Systolic Blood Pressure (mm/Hg)			1	0.99–1.01						
Taking blood pressure medication (yes)			2.23	1.63–3.04						
Presence of Diabetes Mellitus (yes)			0.99	0.66–1.48						
Waist/Hip Ratio			21.77	2.64–179.27			26.69	3.50–203.84		
Framingham Risk Score					1.05	1.04–1.07	1.03	1.01–1.05	1.05	1.04–1.07

* FA is an acronym for fatty acids
The relationships of fatty acids with eGFR were adjusted for all other fatty acids with a p-value 0.2 relationship with eGFR<60mg/dl. The relationships of all demographic and clinical variables were adjusted for all other variables in each model

TABLE 7
Results of Statistical Models with Albumin/Creatinine Ratio >30 and <300 mg/dL as the Outcome

Independent Variable	Logistic Regression Models									
	*FAs		*FAs+Demo/Clin		Framingham Risk Score (FRS)		FRS+ Demo/Clin		FRS+*FAs	
	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI
Fatty Acids										
15:00	0.86	0.71–1.03	1.11	0.90–1.36					1.01	0.84–1.22
16:00	1.11	0.90–1.35	1	0.79–1.26					1.01	0.81–1.26
18:00	0.88	0.73–1.07	0.88	0.71–1.09					0.87	0.71–1.07
16:1 <i>n</i> -7 trans	1.06	0.80–1.41	1	0.74–1.35					0.96	0.71–1.28
18:1 <i>n</i> -6 cis	1.21	0.78–1.88	1.26	0.80–1.99					1.26	0.81–1.97
18:1 <i>n</i> -6 trans	0.83	0.57–1.21	1.16	0.78–1.72					1.06	0.73–1.54
18:1 <i>n</i> -7-9 trans	0.92	0.56–1.53	0.75	0.44–1.27					0.71	0.43–1.17
18:2 <i>n</i> -6 trans/cis	0.78	0.59–1.04	0.81	0.61–1.09					0.79	0.59–1.05
18:3 <i>n</i> -6	1.09	0.93–1.28	1.14	0.95–1.36					1.11	0.94–1.32
20:1 <i>n</i> -9	0.82	0.68–1.00	0.83	0.67–1.02					0.82	0.67–1.00
Demographic Variables										
Race (Caucasian ref group)										
Chinese-American			2.11	1.23–3.61			1.91	1.27–2.87		
African-American			1.31	0.81–2.13			1.31	0.86–2.00		
Hispanic-American			1.34	0.85–2.13			1.31	0.86–2.00		
Age			1.03	1.01–1.05			1	0.98–1.02		
Male			1.27	0.94–1.73			0.49	0.35–0.68		
Clinical Variables										
Smoking (yes)			1.33	0.88–2.00						
non-HDL cholesterol (mg/dL)			1	0.99–1.01						
Systolic Blood Pressure (mm/Hg)			1.03	1.02–1.03						
Taking blood pressure medication (yes)			1.26	0.93–1.72						
Presence of Diabetes Mellitus (yes)			3.12	2.24–4.34						
Waist/Hip Ratio			4.4	0.47–40.85			7.19	0.88–58.89		
Framingham Risk Score					1.08	1.07–1.1	1.09	1.07–1.12	1.08	1.07–1.10

* FAs is an acronym for fatty acids

The relationships of fatty acids with eGFR were adjusted for all other fatty acids with a p-value 0.2 relationship with eGFR <60mg/dl. The relationships of all demographic and clinical variables were adjusted for all other variables in each model.